REMARKS

Prior to this Amendment, claims 1-6, 8-23, and 96-108 were pending in the application. Claims 5, 6, 9-18, 20-23 and 96-108 are withdrawn. Claims 1 and 19 are currently amended and find non-limiting, exemplary support in at least, e.g., paragraphs [0008], [0064], [0066], [0074] and [0196] of the published application US 2005/0196817 A1. No new matter has been presented.

Reconsideration of the application in view of the current claims is respectfully requested and further in view of the following Remarks.

I. INFORMATION DISCLOSURE STATEMENT

Applicants acknowledge, with appreciation, the Examiner's indication that the references submitted in the Information Disclosure Statement filed February 22, 2008 and July 21, 2008 have been considered.

II. OBJECTIONS TO THE DRAWINGS

The Examiner has objected to the drawings for failing to comply with 37 CFR 1.84(p). The Office Action states that the drawings include the following reference characters not mentioned in the description: 5A-5E and 6A-6E, and therefore the amendment filed by applicants on February 22, 2008 was not entered. Applicants have amended the specification herein to refer to the reference characters of Figs. 5A-5E and 6A-6E.

The Examiner has objected to the drawings for failing to comply with 37 CFR 1.84(p)(5). The Office Action states that the drawings do not include the reference sign of "Figure 9" that is mentioned in the description. The Office Action states that there are multiple references to Figure 9 on pages 22 and 23 of the specification. Applicants have amended the specification herein to delete all references to Figure 9.

The Examiner has objected to the drawings for failing to comply with 37 CFR 1.84(p)(5). The Office Action states that the drawings do not include the reference signs of "Figures 11, 12, and 14" that are mentioned in the description. The Office Action states that reference is made to Figures 11, 12 and 14 on pages 19, 34, and 30, respectively. Applicants have amended the specification herein to delete all references to Figures 11, 12, and 14.

Applicants respectfully submit that the objections to the drawings have been rendered moot by the amendments to the specification.

III. CLAIM REJECTIONS UNDER 35 U.S.C. § 112

Claims 1-4, 8 and 19 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Office Action states that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse.

A. Office Action Response to Argument 2

The Office Action states that "while applicant has referred to a definition of sepsis in the art by Bone *et al.*, this is hardly the only definition..." Office Action at page 7.

The Examiner accedes that the Applicants are "free to be his or her own lexicographer and thus may define sepsis in any way they wish." *Id.* Applicants agree and point out that it is settled law that "[d]uring patent examination, the pending claims must be given the broadest reasonable interpretation consistent with the specification. *In re Morris*, 127 F.3d 1048, 1054, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997); *In re Prater*, 415 F.2d 1393, 162 USPQ 541 (CCPA 1969). *See also* MPEP §§ 2111-2111.01. When the specification states the meaning that a term in the claim is intended to have, the claim is examined using that meaning, in order to achieve a complete exploration of the applicant's invention and its relation to the prior art. *In re Zletz*, 893 F.2d 319, 13 USPQ2d 1320 (Fed. Cir. 1989).

While in no way acquiescing to the validity of the rejection in the Office Action, and solely in the interest of expediting prosecution, Applicants have amended claim 1 to be directed to a method of diagnosing severe sepsis in a human subject. Applicants refer Examiner to paragraph [0008] of the published application, which provides the definition of severe sepsis. Applicants point out that the test samples utilized by the methods of the invention in the Examples were obtained from the PROWESS clinical trial. *See* Bernard, et al., Efficacy and safety of recombinant human activated protein C for severe sepsis. NEJM 344:699 (2001) (provided in the Supplemental IDS filed with this Response). In the PROWESS trial, patients were enrolled on the

basis of having documented or suspected infection plus three of the four criteria of systemic inflammation; i.e., fever or hypothermia, leukocytosis or leukopenia, tachycardia, and tachypnea or a supranormal minute ventilation, plus evidence of dysfunction of at least one organ or system. *Id* at 701. In view of the definitions of the specification (also described in Bone *et al.* at page 1646, referred to by Examiner in Office Action at page 7), the clinical samples in the Examples evaluated by the methods of the invention disclosed in the instant application were obtained from patients with severe sepsis. As stated above, claim 1 has been amended to provide a method of diagnosing severe sepsis in a human subject. By this amendment, claims would not, *a priori*, encompass subjects infected with the flu virus, the argument put forth in the Office Action, but would encompass those subjects that meet the definition of severe sepsis, as defined by the specification. Accordingly, one of ordinary skill in the art using the definition of severe sepsis would find the claims to be enabling.

B. Office Action Response to Argument 3

The Office Action states that the claims do not provide a "prognostic panel." Office Action at page 8. Applicants point out that the method of claim 8 requires at least the determination of two markers; i.e., MPIF-1 and TNF-R1, which could be considered a panel that is used for diagnosis of severe sepsis.

C. Office Action Response to Argument 4

The Office Action states that the previously cited references (from the Non-final Office Action of 8/23/2007) show that MPIF-1 and TNF-R1 levels are not predictably correlated with sepsis. Office Action at page 8. Hurst *et al.* is cited in the Office Action as showing that MPIF-1 was elevated in patients with chronic obstructive pulmonary disease, inferring that an elevated level of this marker in this syndrome obviates its usefulness as a diagnostic marker in sepsis. Applicants refer Examiner to Hurst, *et al*, Methods, Table 2 and Results that indicate, amongst other things, that data were obtained only from subjects with COPD and not from control subjects. The data for MPIF-1 in COPD subjects indicate an 18% increase over baseline, a result the authors dismiss as not meeting "the accepted standard." *See* Hurst, page 869.

Applicants refer Examiner to paragraph [0145] of the published application, which states

> Only analytes that fulfilled the following criteria were evaluated as possible sepsis markers: (1) at least one of the group means (either sepsis group or normal

controls) should be greater than 10 when MFI is expressed in log2 scale (>1024 MFI in the linear scale), (2) there should be at least a two-fold difference between the group means, and (3) the p-value for the difference should less than 0.05.

Claim 1 includes the element "wherein the concentration of said analyte in the test sample relative to the reference concentration is *indicative* of the presence of severe sepsis in the human..." (emphasis added). Thus, one of ordinary skill in the art, who reads the claim in view of the specification, would interpret the claim to mean that it should have a difference relative to the reference range concentration on the order of that specified in paragraph [0145] to be "indicative" of sepsis. The Examiner has not provided a basis for a conclusion that the elevation of MPIF-1 disclosed in Hurst *et al* would be interpreted by one of ordinary skill in the art to fall within the scope of claim 1, given the disclosure of the instant specification. Nor has the Examiner provided a basis for a conclusion that an elevation of MPIF-1 in diseases other than sepsis (or severe sepsis) precludes the utility of this marker in the diagnosis of sepsis.

Applicants submit that the conclusory remark that MPIF-1 and TNF-R1 "are not predictably correlated with sepsis" (Office Action at page 8) reflects a selective reading of the cited art that should not be used to undermine the enablement of the claims. The cited references have not been assessed in view of the claims and the criteria established in the instant application. For example, Kimura concludes that mean STNFR p55 concentrations were significantly higher in the infected group than in the uninfected group. *See* Kimura at pg. 1632. Although it is not clear whether these patients had severe sepsis (as defined by the instant application), the use of uninfected but ill subjects as a control group (consistent with method of paragraph [0195] of the instant specification) nevertheless permitted distinction, on a statistically significant basis, of patients with infectious complications from those who were ill but non-infected on the basis of elevated STNFR p55 levels. Similarly, Slotwinski found that while sTNF-R1 was elevated in patients with colorectal surgery, the marker was further increased and was the only marker found to be "a sensitive early marker of local septic postoperative complications," confirming that by using the surgical group as a control, one can utilize elevations in this marker as an indicator of sepsis. *See* Slotwinski at Abstract. Again, Slotwinski does not provide sufficient information to know if these patients meet the definition of severe sepsis utilized in the instant application. Similarly, Dollner found that preterm neonates that were infected in utero (in contrast to the term

neonates that acquired their infections after the birth blood samples were obtained) had significantly higher p55 (TNF-R1) levels than non-infected sick controls. *See* Dollner, Table 4. Thus, one with ordinary skill in the art would, by evaluating markers with reference to appropriate controls, conclude that the data of the references cited in the Office Action consistently demonstrate that TNF-R1 does, in fact, have utility as a marker for infections and/or sepsis.

D. Office Action Response to Argument 5 and State of the Art (pgs 14-15)

The Office Action states (at pg. 15) that no guidance is provided showing the levels of either cytokine (MPIF-1 or TNF-R1) necessary to establish a diagnosis of sepsis or the means to differentiate between increases due to sepsis and those associated with other infections. Applicants submit that Examiner has read an element into the claims that does not exist. Applicants do not claim that either marker is necessary to diagnose severe sepsis. Rather, Applicants claim a method that utilizes these markers to diagnose severe sepsis.

The Office Action states (at pg. 8) that elevated levels of MPIF-1 and TNF-R1 are not indicative of the presence of sepsis and concludes in this paragraph and elsewhere in the Action that the specification shows that the relationship between sepsis and these levels is unpredictable. For example the Office Action points to differences in results for MPIF-1 in study 2 compared to study 1 and study 3 of the Examples and that TNR-R1 was not identified as a candidate marker in studies 1 and 2, concluding that the results are conflicting. Applicants respectfully submit that the conclusion is unwarranted, given the differences in the individual studies and the purpose for those differences. *See* paragraphs [0074], [0079], [0142], [0195] of the published application. In particular, the Applicants refer Examiner to paragraph [0199] of the published application, which explicitly points out the four major differences between study 3 and studies 1 and 2. Studies 1 and 3 were small studies between septic patients and normal controls, and were conducted to identify candidate markers. In study 3, more stringent criteria were used to identify the markers associated with severe sepsis in a substantially larger study of population of patients with a mean APACHE II score of >25, indicating severe sepsis. That these patients had severe sepsis is admitted by Examiner in the Action, at page 14. Importantly, the control group of non-septic but critically ill patients was selected for the express purpose of eliminating markers or marker concentrations that could arise as acute-phase reactants. *See* paragraph [0195] of the published application. The

criteria for identification of biomarkers in study 3 by the methods of the invention are clearly described in paragraphs [0193] and [0195] and the key markers that met the criteria are listed in paragraphs [0196], [0198] and Tables 7 and 8. Thus, the specification provides guidance that would enable one with ordinary skill in the art to establish markers and the concentrations relative to appropriate controls for diagnosis in severe sepsis and, importantly, the means to distinguish severely septic subjects from those with other underlying conditions.

The Applicants hasten to point out that the fact that studies 1 and 2 did not identify TFN-R1 as a marker cannot, without more, serve as a bar to patentability, as inferred in the Office Action. "That claims are interpreted in light of the specification does not mean that everything in the specification must be read into the claims." *Raytheon Co. v. Roper Corp.,* 724 F.2d 951, 957, 220 USPQ 592, 597 (Fed. Cir. 1983), *cert. denied,* 469 U.S. 835 (1984). That TNF-R1 was not identified in studies 1 and 2 was likely due to small sample size and statistics and would be recognized as such by one of ordinary skill in the art. Similarly, one of ordinary skill in the art would understand that the use of more stringent criteria and the substantially larger study population would make the results of study 3 more meaningful for the validation of markers of severe sepsis; the express purpose of study 3. *See* paragraph [0195] of the published application, which states

> Sepsis biomarkers in Study 3 were identified using criteria slightly different than those which were used in Longitudinal Studies 1 and 2. In the previous two sepsis studies, analyte levels in sepsis patients at pre-infusion were compared to analyte levels in healthy individuals to identify analytes elevated in sepsis. These studies identified markers that were not necessarily specific to sepsis since elevated expression levels may have represented acute phase reactants. In an effort to identify markers specific for sepsis, the present study contained comparisons between the sepsis patient group at pre-infusion and a group of equally ill patients that had been admitted to the intensive care unit with a variety of illnesses but who did not have sepsis. The use of sick controls was expected to yield markers with greater specificity for sepsis by controlling for differential expression in acute illness. The sepsis biomarker profile sought in the present study was a significant difference in analyte level between the sepsis patient group during acute sepsis prior to therapy (pre-infusion) and the sick control group. (Emphasis added).

Thus, the methods of the claims are operable, as the results in Example 7 and Tables 7 and 8 confirm.

E. Office Action Response to Argument 6

The Office infers that the various clinical tests mentioned in this section cannot be indicative of the respective conditions and therefore the markers do not have diagnostic value. Applicants respectfully disagree. Applicants refer Examiner to paragraph [0003] of the published application, which states "[s]epsis is diagnosed either by clinical criteria or by culture of microorganisms from the blood of patients suspected of having sepsis plus the presence of features of systemic inflammation." The methods of the instant application utilize markers as clinical criteria that provide key information on the degree of systemic inflammation in a patient suspected of having severe sepsis. Claim 1 recites "[a] method of diagnosing severe sepsis in a human subject, *comprising*: determining a concentration of at least one analyte in a fluid test sample from said human subject; comparing the concentration of each said analyte(s) to a corresponding reference concentration selected to *indicate* the presence or absence of severe sepsis..." (emphasis added). The methods of the claims, given the open transitional term "comprising", when interpreted in light of the specification, permits the use of additional methods such as the culture of microorganisms from the blood or other clinical signs and symptoms to permit one of ordinary skill in the art to arrive at a diagnosis of severe sepsis. Under the conditions of the enabling disclosure, the markers MPIF-1 and TNF-R1, are, in fact, clinical criteria indicative of severe sepsis, as confirmed by the results of study 3.

F. Office Action Response to Argument 7

The Office Action states that the skilled artisan referred to in the previous Response is "unlikely to exist." Office Action at page 10. Applicants respectfully submit that the Office Action applies an incorrect standard to arrive at conclusions that are not substantiated by practice in the art. Applicants refer Examiner to MPEP 2141.03, which states

The "hypothetical 'person having ordinary skill in the art' to which the claimed subject matter pertains would, of necessity have the capability of understanding the scientific and engineering principles applicable to the pertinent art." *Ex parte Hiyamizu*, 10 USPQ2d 1393, 1394 (Bd. Pat. App. & Inter. 1988).

Applicants point out that diagnostic antibodies and biologic reagents that are not "FDA-approved" are nevertheless utilized as analyte specific reagents (ASR's) in diagnostic tests in medical centers throughout the U.S. Applicants refer the Examiner to 21 CFR Sec. 864.4020: Analyte specific reagents.

> Analyte specific reagents (ASR's) are antibodies, both polyclonal and monoclonal, specific receptor proteins, ligands, nucleic acid sequences, and similar reagents which, through specific binding or chemical reaction with substances in a specimen, are intended for use in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens.

Contrary to the statements of the Office Action, such ASR's are, in fact, routinely qualified by CLIA laboratories by validation methods that are well-known in the art, and used by clinicians as diagnostic methods for patients. Such methods cannot be construed as "undue experimentation"; they are a part of daily clinical practice.

With respect to "cut-off" value, one of ordinary skill in the art would realize that the value would be interpreted in light of the guidance provided by the specification and would be obtained, in practice, by the aforementioned validation studies such as those used for ASR's. The FDA guidelines, which are followed by those in the art, provide that such values are to be established by each clinical laboratory.

G. Office Action Response to Argument 8

The Office Action again seizes upon the results from studies 1 and 2 and that fact that TNF-R1 is elevated in other conditions to conclude that the method is not enabled. Applicants submit that consideration of the entirety of the specification does, in fact, support use of the markers MPIF-1 and TNF-R1 in the diagnosis of severe sepsis. Again, paragraph [0195] of the specification makes clear the differences between study 3 and studies 1 and 2. The specification makes clear that the marker concentrations are to be compared to reference concentrations derived from appropriate controls. In addition to study 3, the art cited by the Office Action supports that one can distinguish septic patients from those with underlying conditions, even in cases where such non-septic patients have elevated markers. That a marker is elevated in such underlying conditions does not preclude its utility for other purposes.

H. Office Action Response to Argument 9

The Office Action states "[t]he specification seems to prove that TNF-R1 levels are only elevated when patients have severe sepsis." Office Action at page 11 (emphasis added). Applicants have amended claim 1 to recite "[a] method of diagnosing severe sepsis..."

I. Office Action and Wands Factors

The Office Action has utilized the Wands factors as a component of the enablement rejection. Applicants respectfully disagree with the Examiners interpretation of the following:

Breadth of the Claims:

The claims, as amended, are for a method of diagnosis of severe sepsis, which is defined in paragraph [0008] of the published application, using fluid samples. Applicants submit that the amendments obviate the conclusions that the claims encompass conditions (such as influenza) or samples (such as hair and tissue) that would not be considered appropriate for inclusion by the art.

Guidance of the specification:

The Office Action states that the studies show conflicting results. For the reasons stated above, Applicants disagree. The studies are not comparable one to another because they were designed differently for different purposes, and point to the statement in the Action that study 3 had patients with more severe sepsis than those in studies 1 and 2 as evidence of those differences. Office Action at page 14.

State of the Art:

The studies of the cited art have been discussed above and support Applicant's position that TNF-R1 has utility as a marker for the diagnosis of severe sepsis when compared to appropriate controls. Applicants maintain that the fact that TNF-R1 may be elevated in non-septic patients does not preclude its utility for diagnosis of sepsis. Applicants respectfully disagree with Examiner's statement that a cytokine must be shown to be necessary for diagnosis in order to be useful. Applicants respectfully disagree that the specification has not provided the means to differentiate between the increase in cytokines associated with sepsis and those of other conditions. Study 3 was expressly designed to demonstrate that acute phase markers could be controlled for by

establishing appropriate non-septic patients as controls, with the experimental data of study 3 demonstrating statistically significant increases for MPIF-1 and TNF-R1 in patient with severe sepsis compared to those non-septic patients with underlying conditions.

Applicant's maintain that the specification provides adequate guidance for the practice of the methods of the present invention; that the methods are well within the capabilities of one of ordinary skill in the art and do not require undue experimentation; and that the cited literature supports, rather than undermines, the utility of the markers to detect subjects with severe sepsis even in the face of underlying conditions. Accordingly, applicants submit that a physician of ordinary skill in the art would find the claims, in view of the specification, to be enabling.

Based on the reasons provided above, withdrawal of the rejection under 35 U.S.C. 112, first paragraph, is respectfully requested.

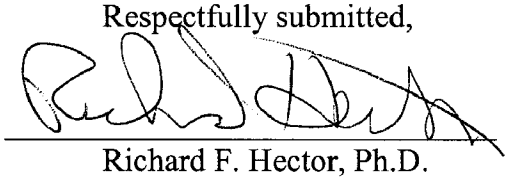
CONCLUSION

Applicants submit that this paper fully addresses the Final Office Action mailed October 9, 2008, and respectfully requests that the Examiner advance the application to issuance. Should the Examiner have any questions, the Examiner is encouraged to contact the undersigned attorney at (650) 849-3017.

FEE AUTHORIZATION

The Commissioner is authorized to charge any additional fees which may be required, including petition fees and extension of time fees, to Deposit Account No. **23-2415** (Docket No. 36671-747.201).

Respectfully submitted,

Date: December 8, 2008 By: 

Richard F. Hector, Ph.D.
Registration No. 51,796

WILSON SONSINI GOODRICH & ROSATI
650 Page Mill Road
Palo Alto, CA 94304-1050
Direct Dial: (650) 849-3017